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PATENT

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In re the Application of: Jiro KANIE

Serial No.: 10/826,165 Group Art Unit: 1618

Filed: April 16, 2004 Examiner: Young, Micah Paul

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For: ENTERAL NUTRITION PRODUCT AND METHOD FOR PREPARING THE SAME

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BRIEF ON APPEAL

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Appendix B4: *Gerontology International Journal of Experimental, Clinical and Behavioural Gerontology*, 2004, pp. 417-419, Vol. 50, No. 6, 2004 (submitted with the Amendment filed 8-29-05).

10. Appendix C - Related Proceeding Appendix
(37 CFR § 41.37 (c)(1)(x))

Real Party in Interest
(37 CFR § 41.37 (c)(1)(i))

The real party in interest in the pending appeal of U.S. Patent Application Serial No. 10/544,431 is Appellant: Jiro Kanie.

Related Appeals and Interferences
(37 CFR § 41.37 (c)(1)(ii))

None

Status of the Claims
(37 CFR § 41.37 (c)(1)(iii))

Claims 1-7 were cancelled in the Amendment filed April 15, 2008.

Claims 8-13 are pending herein, have been rejected, and are under appeal.

Independent claim 8 under appeal is rejected under 35 USC §102(b) over U.S. Patent No. 5,232,733 to Resmer, and under 35 USC §103(a) over Resmer in view of Kabushiki.

Claim 8 was added in the Amendment filed April 15, 2008.

Claim 9 under appeal is rejected under 35 USC §103(a) over Resmer in view of Kabushiki.

Claim 9, which depends from independent claim 8, was added in the Amendment filed April 15, 2008.

Claim 10 under appeal is rejected under 35 USC §102(b) over U.S. Patent No. 5,232,733 to Resmer and under 35 USC §103(a) over Resmer in view of Kabushiki.

Claim 10, which depends from independent claim 8, was added in the Amendment filed April 15, 2008.

Claim 11 under appeal is rejected under 35 USC §102(b) over U.S. Patent No. 5,232,733 to Resmer and under 35 USC §103(a) over Resmer in view of Kabushiki.

Claim 11, which depends from independent claim 8, was added in the Amendment filed April 15, 2008.

Claim 12 under appeal is rejected under 35 USC §103(a) over Resmer in view of Kabushiki.

Claim 12, which depends from independent claim 8, was added in the Amendment filed April 15, 2008.

Claim 13 under appeal is rejected under 35 USC §112, second paragraph, under §102(b) over U.S. Patent No. 5,232,733 to Resmer and under 35 USC §103(a) over Resmer in view of Kabushiki.

Claim 13, which depends from independent claim 11, was added in the Amendment filed April 15, 2008 and amended to correct matters of form so as to properly depend from claim 11, in the Amendment After Final Rejection filed January 15, 2009, which was entered for purposes of Appeal.

Status of Amendments
(37 CFR § 41.37 (c)(1)(iv))

Claims 1-7 were cancelled, and claims 8-13 were added in the Amendment filed April 15, 2008, and claim 13 was amended to correct matters of form in the Amendment After Final Rejection filed January 15, 2009, so as to properly depend from claim 11 in order to overcome the §112, second paragraph rejection. The Advisory Action mailed February 9, 2009 indicated that the 1-15-09 Amendment After Final Rejection was entered for purposes of Appeal.

Summary of Claimed Subject Matter
(37 CFR § 41.37 (c)(1)(v))

The present invention as claimed in independent claim 8, under appeal, provides an enteral nutrition product for enteral administration, not orally, but directly to a stomach or intestines of a dysphagic patient from an external container connected to an external portion of a feeding tube provided through a through-hole of a stoma formed through a portion of the abdominal and stomach walls of the patient upon the application of pressure to the external container (1-24-05 substitute specification, page 6, lines 10-17, paragraph [0017]; page 11, last 2 lines, paragraph [0036] and Figs. 1 and 2). The enteral nutrition product is a semi-solid material having a substantially self-supporting consistency that deforms to flow under an externally applied load without liquefying and that is capable of containing a higher concentration of a nutrient component than a liquid (1-24-05 substitute specification, page 6, lines 21-27, paragraph [0018]). The semi-solid material comprises a mixture of a liquid nutrient solution and a semi-solidifying agent comprising agar (1-24-05 substitute specification, page 6, line 21, paragraph [0018]) that is added to the liquid nutrient solution in a predetermined ratio sufficient to ensure that the self-supporting consistency of the semi-solid enteral nutrition product remains substantially unchanged before, during, and after enteral administration of the semi-solid enteral nutrition product into the patient (1-24-05 substitute specification, page 7, lines 3-5, paragraph [0019]). The self-supporting consistency of the semi-solid enteral nutrition product is further maintained within the stomach or the intestines of the patient such that the semi-solid enteral nutrition product does not liquefy due to the body temperature of the patient (1-24-05 substitute specification, page 7, lines 5-8, paragraph [0019]), to thereby prevent the patient from experiencing gastro-esophageal reflux (1-24-05 substitute specification, page 9, lines 21-24, paragraph [0028] and Fig. 4).

The semi-solidifying agent according to the present invention serves to increase the consistency of the nutrient liquid (i.e., thicken) such that the resulting semi-solid mixture has a substantially self-supporting consistency that is like a solid in that the mixture is stiff enough to define a shape that is not spontaneously reduced under atmospheric conditions. That is, a distinct shape assumed by the semi-solid mixture will be maintained after that mixture has been removed from the mixing

container. This structural characteristic is unlike a liquid or semi-liquid, which will not maintain any specific shape after being removed from its container, and which instead flow to assume the shape of the new container or to spread outwardly if not otherwise confined. In other words, the consistency of the semi-solid mixture contributes to its distinct structural characteristics that enable the semi-solid mixture to be formed into a shaped form that is self-supporting and which will not otherwise significantly deform without the application of an externally applied force thereto (1-24-05 substitute specification, page 10, last 3 lines – page 11, line 12, paragraph [0032]). The distinct consistency characteristic of the semi-solid mixture also allows the shaped mixture to experience deformation as need, for example, to translocate from a container into a feed tube, but only under an applied pressure load. While the "shape" of the mixture may change under pressure with respect to the actual shape of the containers and the feed tube, the substantially self-supporting consistency of the semi-solid mixture does not substantially change while the enteral nutrition product is administered via the feeding tube, and the shaped form is maintained even after the enteral nutrition product is administered into the body of the patient (Id.).

Further, the distinct semi-solid consistency of the mixture constituting the enteral nutrition product is maintained even when the semi-solid enteral nutrition product is subjected to the temperatures of the enteral environment (i.e., the stomach and intestines of the body) that would otherwise lead to liquefaction of prior art tube food mixtures due to body heat (1-24-05 substitute specification, page 11, lines 16-20, paragraph [0034], page 12, lines 3-7, paragraph [0037]). Because the semi-solid enteral nutrition product according to the present invention maintains this self-supporting, yet deformable, semi-solid form, even within the patient, the enteral nutrition product will not flow, or back flow, like a liquid within the stomach and/or intestines of the patient. In that manner, the occurrence of a dysphagic patient experiencing regurgitation or reflux is significantly reduced, if not eliminated, which is beneficial to patients and caregivers alike (1-24-05 substitute specification, page 37, lines 10-13, paragraph [0137]). This critical benefit is particularly important for patients who cannot sit up or are otherwise restricted to a supine position, which makes them especially susceptible to the regurgitation and reflux problems commonly recognized and experienced in connection with enteral nutrition substances according to the prior art.

The unique and previously unrealized structural characteristics of the claimed enteral nutrition product prevents the enteral nutrition product from refluxing back toward the esophagus, even after the enteral nutrition product is administered to a portion of the patient other than the esophagus, such as the stomach of a patient whose cardia has been deteriorated in function. This feature of the present invention is critical because it has been shown that gastro-esophageal reflux ("GER") of prior art enteral nutrition products is likely to cause diseases such as reflux esophagitis or aspiration pneumonitis (1-24-05 substitute specification, page 3, lines 18-27, paragraph [0008], page 4, lines 1-9, paragraph [0009], page 4, lines 16-24, paragraph [0011] and Fig. 5). The enteral nutrition product according to the claimed invention effectively prevents such gastro-esophageal reflux, and effectually prevents reflux esophagitis and aspiration pneumonitis, which makes it clear that the enteral nutrition product offers many health and medical benefits aside from its nutritional value that have not been provided heretofore.

Grounds of Rejection to be Reviewed on Appeal (37 CFR § 41.37 (c)(1)(vi))

Whether claims 8, 10, 11 and 13 are unpatentable under 35 USC § 102(b) over U.S. Patent No. 5,232,733 to Resmer (hereinafter referred to simply as Resmer), and whether claims 8-13 are unpatentable under 35 USC § 103(a) over Resmer in view of Kabushiki.

Arguments
(37 CFR § 41.37 (c)(1)(vii))

A. Resmer fails to disclose or suggest each and every feature in independent claim 8, and therefore, the §102(b) rejection of claims 8, 10, 11 and 13 over Resmer is improper and should be withdrawn.

Appellant respectfully submits that, contrary to the PTO's assertions, Resmer fails to disclose or suggest each and every feature in independent claim 8 for at least the reasons explained below.

The PTO asserted that "the [Resmer] patent meets each of the compositional limitations of the claims namely it discloses an enteral feeding tube composition comprising a nutrient liquid and a semi-solidifying agents. By meeting these limitations any composition would inherently meet the functional limitations since those limitations would fall naturally from the properties of the components" (7-16-08 Office Action, page 3, last 5 lines). Appellant respectfully submits that the PTO is incorrect.

The alleged "functional limitations" of claim 8 are not functional limitations at all, but are instead tangible descriptions of the physical, structural characteristics of the claimed enteral nutrition product, namely the unique consistency of the enteral nutrition product and its capacity to retain its particular consistency characteristics under specific conditions that are otherwise known to affect the consistency of prior art formulations. Appellant respectfully submits that the PTO's position is predicated on a lack of knowledge of the actual properties of agar, and is merely based on the incorrect premise that the presence of a given concentration of agar would automatically and without exception provide a resultant structure exhibiting in the structural limitations set forth in independent claim 8. Appellant respectfully submits that one skilled in the art would readily appreciate and understand that the mere presence of some form of agar does not necessarily, and would not be expected to automatically result in the same novel and non-obvious consistency characteristics defined in independent claim 8.

1. Resmer is the very type of prior art discussed in the present specification that is known to suffer from the drawbacks that are advantageously eliminated by the specifically claimed structural characteristics of the present invention.

Resmer discloses a drink and tube *solution* that includes guar-flour as a thickening agent, and which includes other stabilizing components to ensure that the guar-flour thickening agent does not precipitate out of the solution over time. Resmer specifically discloses that the product is sterilized and homogenized *emulsion* (See Resmer, Col. 4, lines 27-34). Resmer also discloses that the viscosity of the solutions for tube feeding is about 70 cp at 25°C. One skilled in the art would readily appreciate that, while thickened, solutions and emulsions having such a viscosity are still solutions and emulsions that are understood to exhibit liquid characteristics, as opposed to the characteristics of solids, and would not be sufficiently solid to exhibit the claimed semi-solid consistency characteristics or prevent the possibility of reflux.

2. Resmer fails to disclose an enteral nutrition product for enteral administration, not orally, but directly to a stomach or intestines of a dysphagic patient from an external container connected to an external portion of a feeding tube provided through a through-hole of a stoma formed through a portion of the abdominal and stomach walls of the patient upon the application of pressure to the external container.

When used in conjunction with a feeding tube, Resmer's formulation is designed to be administered through a feeding tube at a viscosity of 70 cp. In light of the absence of any teaching to the contrary, Appellant respectfully submits that one skilled in the art would reasonably interpret Resmer's tube food to be a common nasogastric tube food, which is administered to an intubated patient through an open end of a tube provided in a patient's mouth or nose, for example. One skilled in the art can readily appreciate the fact that different factors must be considered with respect to ordinary nasogastric intubation, like that of Resmer, opposed to the particular factors associated with the gastronomy feeding according to the present invention. There is no disclosure in Resmer whatsoever about the possible applicability of the tube food with respect to gastronomy feeding, which involves the administration of the tube formulation directly to a stomach or intestines of a dysphagic patient from an external container connected to an external portion of a feeding tube provided through a through-hole of a stoma formed through a portion of the abdominal and stomach walls of the patient, as claimed.

3. Resmer fails to disclose an enteral nutrition product for enteral administration having a semi-solid material having a substantially self-supporting consistency that deforms to flow under an externally applied load without liquefying.

In order for an enteral nutrition product to be considered a "semi-solid material," in the context of claim 8, the enteral nutrition product is required to exhibit self-supporting consistency characteristics. That is, the enteral nutrition product is required to have a nature such that its physical form remains substantially unchanged unless and until a compulsory external force is loaded thereto. A close technical relationship exists between the enteral administration of the enteral nutrition product via the feeding tube under pressure, and the substantially self-supporting consistency of the enteral nutrition product that deforms to flow under an externally applied load. That is, if an additional pressure or force is not externally applied to the semi-solid enteral nutrition product present within the container, then because the semi-solid enteral nutrition product is harder than a liquid, the semi-solid enteral nutrition product fails to deform and does not smoothly flow through the feeding tube, which typically has an even smaller diameter than the mouth or esophagus of the patient.

These features are simply not disclosed or suggested in Resmer, and the claimed features are not an inherent characteristic of prior art tube foods such as that disclosed in Resmer. In fact, prior to the present invention, the specifically claimed consistency characteristics and the advantageous benefits attributable thereto were not known, and would not have been expected to be successfully applicable in ordinary tube feeding situations. The conventional formulation disclosed in Resmer is nothing more than a thickened liquid that can be pump-fed through a tube, and though thickened, clearly lacks the heretofore unknown substantially self-supporting consistency characteristic of the present invention. One skilled in the art would not have had any reasonable expectation that the conventional tube food disclosed in Resmer would possibly exhibit the claimed substantially self-supporting consistency characteristics.

4. Resmer fails to disclose an enteral nutrition product for enteral administration having a self-supporting consistency of the semi-solid enteral nutrition product remains substantially unchanged before, during, and after enteral administration of the semi-solid enteral nutrition product into the patient and that the undisclosed self-supporting consistency of the semi-solid enteral nutrition product is further maintained within the stomach or the intestines of the patient such that the semi-solid enteral nutrition product does not liquefy due to the body temperature of the patient.

This feature is simply not disclosed or suggested in Resmer, and this claimed feature is not an inherent characteristic of prior art tube foods such as that disclosed in Resmer. To the contrary, Resmer discloses that the viscosity of the solutions for tube feeding is about 70 cp at 25°C. One skilled in the art would readily understand that a viscosity of 70 cp at 25°C is not semi-solid, as claimed, but rather a thick solution having solution and emulsion characteristics, which is designed and intended to deform to flow, even without the application of external pressure.

Moreover, is commonly understood that 25°C converts to 77°F, which is 21.6 °F *less than normal body temperature* of 98.6°F. Even if the Resmer's solution exhibits a consistency so as to have a viscosity of 70 cp at 25°C, one skilled in the art would readily expect that the viscosity would decrease at least somewhat within the internal environment of the body, in view of a temperature increase of more than 20 °F. In any event, one skilled in the art would not expect that the viscosity of the tube food in Resmer would be sufficient to exhibit the self-supporting characteristics at room temperature (25°C ,77°F), much less at body temperature (98.6°F).

Appellant respectfully submits that, prior to the present invention, the specifically claimed consistency characteristics and the advantageous benefits attributable thereto were not known. One skilled in the art would not have had any reasonable expectation that the conventional tube food disclosed in Resmer could possibly exhibit the claimed consistency characteristic before otherwise undisclosed direct enteral administration, much less maintain those otherwise undisclosed and unexpectedly advantageous characteristics during and after enteral administration of the thickened liquid formulation into the stomach or intestines of a dysphagic patient.

5. Resmer fails to disclose an enteral nutrition product for enteral administration that is specifically formulated to have any specific characteristics sufficient to prevent the patient from experiencing gastro-esophageal reflux.

Resmer does not recognize the problem that is solved by the present invention, namely the dangers and drawbacks associated with the common occurrence of gastro-esophageal reflux in dysphagic patients, much less address any manner by which its formulation could possibly overcome the otherwise unrecognized problem in the particular class of patients to which the present invention applies. Resmer is nothing more than a conventionally thickened liquid tube food whose common characteristics represent one aspect of the state of the art that has been improved by the present invention. The thickened consistency of the solutions in Resmer is intended to slow the absorption of the nutrients so as to help equalize the blood sugar levels of diabetic patients (See Resmer, Col. 1, lines 9-16). The stability is imparted to Resmer's solution by the combination of the thickening agent and the stabilizing agent, however, there is no disclosure or suggestion in Resmer that any characteristic of the solution would be sufficient to prevent gastro-esophageal reflux.

Appellant respectfully submits that the basic and novel characteristics of the present invention recited in independent claim 8 are not present, expressly or inherently, in the diet formulations according to Resmer.

B. The §103(a) rejection of claims 8-13 over Resmer in view of Kabushiki should be withdrawn because Resmer fails to disclose each and every feature of the present invention for the same reasons described above, because Kabushiki does not overcome the deficiencies of Resmer, and in view of the evidence of secondary considerations that clearly establish the non-obviousness of the claimed enteral nutrition product.

1. Resmer fails to disclose each and every feature of the present invention for the same reasons described above, and Kabushiki does not overcome the deficiencies of Resmer.

Appellant respectfully submits that Resmer does not disclose each and every feature recited in independent claim 8 for at least the reasons explained above. Furthermore, Resmer does not provide any teaching or suggestion that could have possibly led one skilled in the art to try to modify Resmer so as to provide an even thicker solution exhibiting any semi-solid characteristics, much less the specifically

claimed semi-solid characteristics, which, prior to the present invention, would not have been expected to yield successful results in conjunction with tube feeding, much less any beneficial results. Kabushiki, which was applied with respect to its disclosure of a tube feeding apparatus, does not overcome the deficiencies of Resmer.

Furthermore, Appellant respectfully submits that none of the applied references are directed to providing an enteral nutrition product to a dysphagic patient specifically to prevent that dysphagic patient from experiencing and suffering from gastro-esophageal reflux, as claimed. Further still, Appellant respectfully submits that none of the applied references disclose or even remotely suggest that there is, or even could be any particular relationship between an enteral nutrition product having a self-sustaining consistency and the prevention or reduction of gastro-esophageal reflux. Indeed, such a relationship has remained unknown and unrecognized prior to the present invention.

2. The PTO must consider the evidence of unexpected results and other secondary considerations associated with enteral nutrition product according to the present invention, which is sufficient to rebut the PTO's *prima facie* case of obviousness against the present invention defined in the pending claims.

The Appellant, who is a Japanese gastroenterologist, has successfully provided medical treatments to patients at his own hospital using the products according to the claimed invention. Prior to filing the present U.S. patent application, Appellant filed a corresponding Japanese patent application that is substantially identical to the claimed invention pending herein, and which has already been patented in Japan as Japanese Patent No. 3516673.

Moreover, Appellant has co-authored several medical reports relating to the claimed invention, which have been published in several well-known medical publications. Copies of two related articles, which are attached hereto as Appendices B3 and B4 in Evidence Appendix B, include: "Prevention of Late Complications by Half-Solid Enteral Nutrients in Percutaneous Endoscopic Gastrostomy Tube Feeding" *Gerontology International Journal of Experimental, Clinical and Behavioural Gerontology*, pp. 417-419, Vol. 50, No. 6, 2004; and "Prevention of gastro-esophageal reflux by an application of half-solid nutrients in patients with percutaneous endoscopic gastrostomy feeding" *Journal of the American Geriatrics Society*, pp. 466-467, Vol. 52, Issue 3, March 2004.

The attached publications concretely demonstrate that the present invention has been recognized by skilled artisans as being a substantial contribution in the field of gastroenterology, and further, that the present invention provides recognized medical benefits, beyond nutritional benefits, in real-life clinical applications. Appellant respectfully submits that the attached publications tangibly prove that skilled artisans have recognized the novelty, non-obviousness, clinical importance and practical value of the achievements made by Appellant with respect to the present invention. Appellant respectfully submits that such peer recognition objectively demonstrates that the present invention is not merely an obvious combination of common pudding or cream or any other prior art.

In addition to the above, Appellant respectfully submits that the claimed invention provides unexpected results, and unexpected benefits, in providing a semi-solid enteral nutrition product that effectively prevents the occurrence of gastro-esophageal reflux in dysphagic patients. The experimental results presented in the present specification demonstrate the unexpected nature and criticality associated with the specifically claimed ratios, concentrations and compositions according to the present invention. Such unexpected results establish the non-obviousness of the present invention and must be considered by the PTO.

Attached in Appendix B1 in Evidence Appendix B are copies of two Japanese medical treatises and corresponding English translations of the relevant portions thereof, which further prove that the semi-solid enteral nutrition product and administration device according to the present invention have been recognized among skilled artisans in the medical community. These publications recognize that the present invention provides unexpected and beneficial results which meet a long-felt, but heretofore unfulfilled need with respect to providing sufficient nutrition for dysphagic patients without creating additional complications attributed to gastro-esophageal reflux.

The Rule 132 Declaration submitted on April 15, 2008, a copy of which is attached hereto in Appendix B2 of Evidence Appendix B, also includes tangible evidence of secondary considerations that concretely demonstrate the novelty and non-obviousness of the present invention. The Declaration establishes that the present invention has been recognized as novel and non-obvious and has been patented in Japan. The Japanese patent corresponding to the present invention has been licensed for commercial purposes, and its commercial viability is further verified to by the

ongoing negotiations to establish additional licenses. The importance, novelty and non-obviousness of the present invention has also been recognized and praised by Applicant's peers in numerous publications. These publications along with the Japanese patent and the license(s) therefore also demonstrate that the present invention solves a long-felt but heretofore unresolved need.

Applicants respectfully submit that the PTO must properly consider such secondary considerations, and that the evidence of secondary considerations presented herein is sufficient to rebut the PTO's *prima facie* case of obviousness against the present invention defined in the pending claims.

For at least the reasons explained above, Appellant respectfully submits that the prior art of record fails to disclose or suggest each and every feature recited in independent claim 8. Accordingly, Appellants respectfully submit that all claims pending herein define patentable subject matter over the prior art of record, and respectfully request that the pending rejections be reconsidered and withdrawn.

Respectfully submitted,

March 16, 2009

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Claims Appendix
(37 CFR § 41.37 (c)(1)(viii))

1-7. (Cancelled)

8. (Previously Presented) An enteral nutrition product for enteral administration, not orally, but directly to a stomach or intestines of a dysphagic patient from an external container connected to an external portion of a feeding tube provided through a through-hole of a stoma formed through a portion of the abdominal and stomach walls of the patient upon the application of pressure to said external container, said enteral nutrition product comprising:

a semi-solid material having a substantially self-supporting consistency that deforms to flow under an externally applied load without liquefying and that is capable of containing a higher concentration of a nutrient component than a liquid,

wherein said semi-solid material comprises a mixture of a liquid nutrient solution and a semi-solidifying agent comprising agar that is added to said liquid nutrient solution; and

wherein said mixture comprises said semi-solidifying agent and said liquid nutrient solution in a predetermined ratio sufficient to ensure that said self-supporting consistency of said semi-solid enteral nutrition product remains substantially unchanged before, during, and after enteral administration of said semi-solid enteral nutrition product into the patient, and said self-supporting consistency of said semi-solid enteral nutrition product is further maintained within the stomach or the intestines of the patient such that said semi-solid enteral nutrition product does not liquefy due to the body temperature of the patient, to thereby prevent the patient from experiencing gastro-esophageal reflux.

9. (Previously Presented) The enteral nutrition product according to claim 8, wherein said feeding tube has an internal diameter that is larger than approximately 4 mm.

10. (Previously Presented) A method for preparing the semi-solid enteral nutrition product according to claim 8, comprising the steps of:

providing a holder comprising said container;

filling said holder with said mixture of said liquid nutrient solution and said semi-solidifying agent in a liquid state thereof; and

cooling said mixture within said holder, together with said holder, to thereby prepare said enteral nutritional product.

11. (Previously Presented) An enteral nutrition product administration device comprising:

a holder; and

the enteral nutrition product according to claim 8 provided within said holder;

wherein said holder comprises said container; and

wherein said enteral nutrition product is prepared by a method comprising the steps of:

providing said holder;

filling said holder with said mixture of said liquid nutrient solution and said semi-solidifying agent; and

cooling said mixture within said holder, together with said holder, to thereby prepare said enteral nutrition product.

12. (Previously Presented) The enteral nutrition product according to claim 8, wherein said semi-solidifying agent comprising agar is added in amount of 1 gram to 200 ml of a diluting liquid that is added to said liquid nutrient solution.

13. (Previously Presented) The enteral nutrition product administration device according to claim 11, containing a required amount of the enteral nutrition product per one batch of administration which is fed into the patient via the feeding tube.

Evidence Appendix

(37 CFR § 41.37 (c)(1)(ix))

Appendix B1: Japanese Medical Treatises 1 and 2 and English translations of relevant portions thereof (related arguments submitted in the Amendment filed 5-11-06).

Appendix B2: Rule 132 Declaration of Jiro Kanie and its related attachments (submitted with the Amendment filed 4-15-08)

Appendix B3: *Journal of the American Geriatrics Society*, March 2004, pp. 466-467, Vol. 52, Issue 3, March 2004 (submitted with the Amendment filed 8-29-05)

Appendix B4: *Gerontology International Journal of Experimental, Clinical and Behavioural Gerontology*, 2004, pp. 417-419, Vol. 50, No. 6, 2004 (submitted with the Amendment filed 8-29-05).

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APPENDIX B1

C.C.Report

経口での食事摂取が困難な人々に経皮内視鏡的胃瘻造設術が急速に普及し、在宅ケアにおいてなくてはならないものになっていますが、液体経腸栄養剤を使用する際には、下痢をはじめとして、いくつかの問題が残っています。栄養剤を寒天により固形化することで、その改善を試みた事例を紹介します。

経管栄養剤の固形化による利用者のQOLの向上

藤田 和枝 Fujita Kazue
青葉区メディカル訪問看護ステーション
看護師

〈事例〉

Eさん（54歳）女性。脊髄小脳変性症。夫との2人暮らし。夫は会社員のため日中独居。15年ほど前に発症し、歩行障害出現。1995年頃から歩行不能となる。嚥下困難も徐々に進行し、2000年には食物を詰まらせ窒息状態となり、誤嚥性肺炎も併発したため胃瘻造設術施行。現在マイクロベーシブボタン24Frを挿入している。日常生活は全介助。発語できず、うなずきや表情でコミュニケーションをとっている。

固形化前の栄養摂取と排便

Eさんはエンシュア H1.5（375mℓ）缶を、朝・夕各1回滴下方式にて注入していた。平日は訪問看護師が経管栄養を施行し、引き続きヘルパーが滞在して見守りを行っていた。注入時間はヘルパー滞在時間に合わせて、平均130分に設定し、週末は夫が平均165分の注入時間で施行していた。週末のほうが排便回数は少なかったものの、平日・週末での便性状の違いは見られなかった。

経管栄養剤固形化前の排便の平均回数は1日2.2回であったが、多い日は6回もの排便があった。普通便の排泄は見られず、水様便や泥状便がほとんどであった。経管栄養を注入するとまもなく水様性の排便があるため、車椅子上で大きな紙オムツを腰部に巻きつけた状態で注入する方法をとっていた。

固形化前の問題点を下記に挙げる。

①水様便を主とした頻回な下痢と、それによる褥創形成や肛門周囲の皮膚糜爛および水分や電解質、栄養分の喪失の恐れ

②滴下中、ヘルパー見守り時に起こる滴下不良や漏れ、嘔気の出現といったトラブルの発生（看護師の緊急訪問にて対応）

③栄養剤注入中の体動制限による褥創発生および悪化。動けないことによる本人のストレス

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なかなか改善されない下痢

滴下方式において栄養剤注入をゆっくり行い、胃内停滞時間を長くすることで下痢が改善することが知られている。Eさんも肺炎で入院中、下痢の改善に「持続注入ポンプ」の利用が効果的であったため検討を行ったが、安静状態であった入院中と違い、ベッド上臥床と車椅子起座位の移動を日に数回行うために取り扱いの点で問題があった。また日中1人でいる時間があるので、チューブをつなげたままでは外れ・漏れ・詰まりなどの不安がある。つながれているという感覚もさらに強まってしまうなど、種々の問題があるため実際に行うことは断念した。

嶋尾[1]らは、下痢の改善には1缶(250mℓ)当たり150分に延長するよう勧めている(100mℓ/時)。Eさんも休日の注入時間を平日の130分から165分に延ばしていたが、排便回数は多少少なくなったものの便性状の改善にはならなかった。

注入回数を2回から3回に増やす方法も試みたが、訪問看護対応時間内では注入間隔が狭まるためか栄養剤の逆流や消化不良を起こした上に排便状況も改善されなかった。また栄養剤滴下時間延長目的でのヘルパー滞在時間の変更は難しく、止痢剤の投与もほとんど効果がなかった。

経管栄養固形化への実際

そこで蟹江[2)~5)]らが紹介している経管栄養を固形化して注入する方法が効果的ではないかと考え、これを検討した。この方法は胃内停滞時間を延長することで下痢を改善する以外にも、胃から食道への逆流が減少するため嘔吐や誤嚥性肺炎の予防効果がある。また注入時間の減少により介護者の負担が減るとともに体動制限も少なくなる。

一方、固形化を在宅で行うには、栄養剤の固形化の調理を誰が行うのか、夫や他サービスの協力を得ることができるかといった問題点が考えられた。

まず、夫へ固形化のメリットを示し協力を求めた。「今までいろいろな方法を試しても改善されなかった下痢が改善される可能性があるならば、試してみたい」と夫は快諾してくれた。栄養剤の固形化も夫が行うこととなった。

訪問看護滞在中に経管栄養注入が終了するため、ヘルパーの見守り中のトラブル発生の心配がなくなる。また、時間的余裕もできたため、ヘルパーからも寒天作り(コラム参照)の協力を得ることができた。注入はカテーテルチップを用い、1回10分程度で行った。

導入初期は朝の栄養剤半缶分を固形化し、残り1缶分を通常の滴下注入をした。そしてEさんの状態を確認しながら固形化の割合を徐々に増やし、約1カ月後に朝の注入分をす

固形化による胃瘻部からの経管栄養注入法[2)~5)]

【栄養剤固形化の調理手順】

①20mℓ程度の冷水と「ばば寒天」2gを混合し撹拌、寒天を水になじませる

②上記寒天水にポットのお湯200mℓ(80℃以上)を入れかき混ぜる

③人肌に暖めた(50℃以下)エンシュアH 250mℓに②の寒天溶液を混合し撹拌する。エンシュアHの温度が低いと混合中から寒天が固まってしまうため、栄養剤を暖めてから混ぜる必要があるが、成分変性を起こさないために50℃以下とする

④冷所で保存し凝固させる

【注入方法】

容器に作製した栄養剤を、カテーテルチップで吸引し注入する

導入当初の1回の注入時間はAさんの様子を見ながら10分以上かけて行い、途中で苦痛表情や腹部膨満、抵抗等を感じた場合は中止する(現在は平均7~8分前後で注入し終えている)

注入後は白湯にてフラッシュを行い、チューブ内の詰まりや栄養剤の貯留を防止する

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べて固形化した。夕は固形化せず、これまでどおりすべての栄養剤を通常の滴下注入とした。

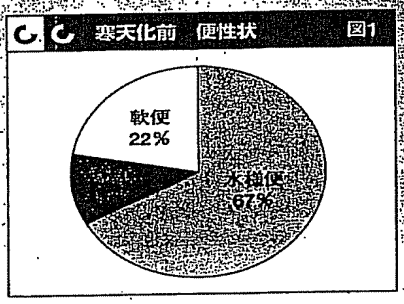
この方法を続けていたところ、嘔気や消化不良が見られるようになった。これは注入量が消化スピードに対し多すぎるためと考え、主治医と相談し、1日の注入量を3缶から2.5缶に減らすことにした。また消化時間を長くするため夫に帰宅後の注入を依頼し、注入回数を1日2回から1日3回（朝1缶・夕1缶・夜半缶）に変更した。ただし、脱水予防のため朝のみ通常の滴下方式とした。

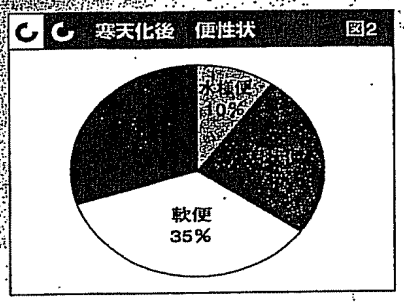
固形化後の変化と考察

便回数は1日平均2.2回から1.6回に減少した。また、固形化以前には普通便は全く見られなかったが、固形化後は普通便が見られるようになり、普通便と軟便を合わせた割合が65%に増加した（図1、2）。便の性状が著しく良化したことで、肛門周囲の皮膚糜爛や褥創が減少した。

さらに、注入時間が短いため本人の「つながれている」という感覚も減った上、空いた時間で外出もできるようになった。

夫も滴下方式では時間がかかるために、平日の経管栄養注入を訪問看護師にすべて任せていたが、短時間でできる寒天注入方式ならば帰宅後の注入が可能となった。平日の夜、夫が経管栄養注入することで、注入間隔を十分に取ることができるようになり、栄養剤の逆流や消化不良も見られなくなった。





経管栄養の固形化は、これまでEさんの最大の苦痛であった下痢と、それに伴う合併症からの解放を可能にし、介護者の負担軽減にもつながった。私たちも固形化による排便の変化を目の当たりにし、その効果に大変驚いている。

しかしその一方で、在宅で取り入れるには問題点もある。

その1つが、「家族の協力」の問題である。Eさんの場合、大きな問題であった下痢の改善が明らかだったことで夫の協力も得やすかった。だが別の事例では、家族が期待するほどの効果をすぐに感じられず、寒天作りが負担と感じられ断念した例や、胃瘻用カテーテルの代わりに元来詰まりやすい尿道カテーテルを使用して、詰まりが起こり、家族から継続を断られた事例があった。

在宅においては、本人と家族が自ら介護や治療方針を決定することが基本である。新たなケア方法を取り入れる際、準備はもちろん、アプローチやサポートの仕方が大変重要になる。それらが不十分な場合、効果に期待がもてても、受け入れや継続が不可能となってしまうことがある。

経管栄養の固形化は、経管栄養の抱える多くの問題を解消できる可能性をもっている。これらの事例を踏まえ、今後は固形化が受け入れやすく、多くの方がメリットを受けられるような取り組みが必要である。

●参考文献
1) 嶋尾仁：胃瘻（PEG）造設患者のケアマニュアル，医学芸術社，2000.
2) 蟹江治郎：固形化経腸栄養剤の投与により胃瘻栄養の慢性期合併症を改善した1例，日本老年医学会雑誌，第39巻第4号，p448-451，2002.
3) 蟹江治郎：胃瘻PEGハンドブック，第1版，医学書院，p117-122，2002.
4) 蟹江治郎：経腸栄養剤固形化によるPEG後期合併症への対策，臨床看護，第29巻第5号，p664-670，2003.
5) PEGドクターズネットワーク：PDN通信，創刊号～第3号，http://www.peg.ne.jp/.

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TRANSLATION OF TREATISE NO.1

TITLE OF TREATISE: Separate volume of monthly magazine "COMMUNITY CARE," Vol. 5, No.10, written in Japanese, published October 2003

TITLE OF ARTICLE: "IMPROVEMENT IN USERS' QOF OWING TO SEMI-SOLIDIFIED TRANSLUMINAL NUTRITION," pp. 53-55 of the separate volume

AUTHOR: Ms. Kazue Fujita, a nurse

TRANSLATIONS OF TWO EXCERPTS:

Then, it was found that a method which had been introduced by Mr. Kanie, et al., in which transluminal nutrition, upon semi-solidified, was administered via tube was possibly effective, and this method was verified. This method offers not only an advantage that a resulting extension of a time during which the nutrition can be stayed within the stomach promotes recovery from diarrhea, but also an advantage that suppression in the reflux from the stomach to the esophagus prevents vomiting and aspiration pneumonitis. This method further offers an advantage that a resulting decrease in a time required for administration reduces care givers' responsibilities and relaxes the constraint on allowable movement of the patient during administration.

The semi-solidification of transluminal nutrition

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enabled Mr. M to release from diarrhea, which had been the most painful to Mr. M, and to release from complications resulting from diarrhea, conducive to relaxation in care givers' responsibilities. We saw with our own eyes the changes in defecation resulting from the semi-solidification, and we were very surprised with the effects.

Notes: In this tretise, "Mr. Kanie" is the inventor of the claimed invention of the present application, and the "semi-solidification" is a technique according to the claimed invention.

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PEG造設後の栄養管理

TREATISE No.2

宮澤　靖　医療法人近森会　栄養科
Miyazawa, Yasushi

経腸栄養法の特徴と方法，栄養管理，
経腸栄養剤固形化

適正栄養管理法の選択

PEG造設症例に対して，まず栄養評価を行い栄養学的な解析に基づいた適切な栄養管理法を選択し，担当医に提言することが要求される．経口摂取が十分できる症例には，病態や栄養状態に応じて食事の内容や量などを指示するが，経口摂取が困難だったりそれが不適切な病態においては図1に示すような指針に従って栄養管理法を選択する．これは米国静脈経腸栄養学会（A.S.P.E.N.）のガイドラインを一部改変したものである[1]．これによると経腸栄養法を行う対象は，消化管の使用が可能な全症例となる．しかし一般的には，このような指針がいまだ十分に浸透していないのが現状である．ただ「食べられないからPEGにすればいい，静脈栄養にすればいい」のではなく，正しい栄養評価に基づいて望ましい時期に造設することが肝要である．

瘻管法（胃瘻，腸瘻等）による栄養投与は，第一に患者の消化管が安全に使用できるかを検討する．表1に示す項目が経腸栄養法の主な適応となる項目なので，これらに該当する症例か検討し，第2段階として経腸栄養法に依存する期間はどのくらいなのか評価する．仮に6週間以上経腸栄養法に依存しなくてはならない症例については，瘻管法を選択とする．

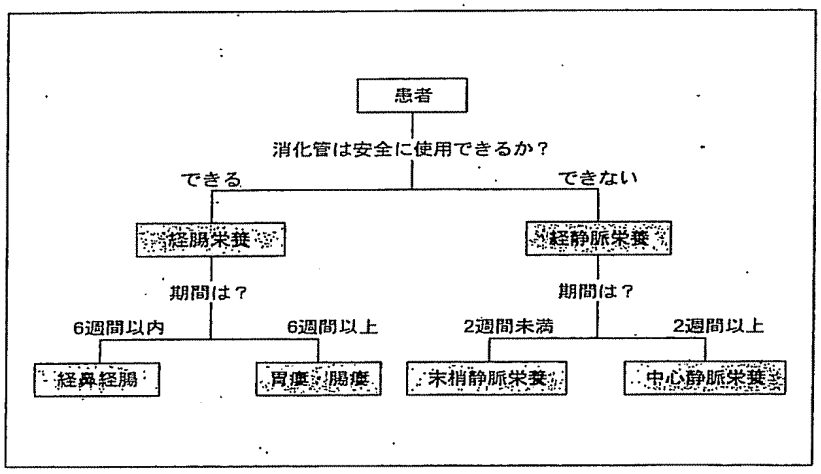

図1　栄養管理法の選択

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表1　経腸栄養法の主な適応

1．経口摂取不能または不十分例
　1）上部消化管通過傷害（食道がん，喉頭がんなど）
　2）手術直後
　3）放射線療法，がん化学療法施行例
　4）意識障害
　5）がん末期
　6）神経性食思不振症
2．経口摂取が不適切な場合
　1）上部消化管出血
　2）上部消化管術後縫合不全，消化管外瘻
　3）亜イレウス
3．炎症性腸疾患
　　クローン病，潰瘍性大腸炎
4．吸収不良症候群
　　短腸症候群，放射線腸炎，慢性膵炎
5．肝障害，腎障害
6．重症熱傷
7．その他
　　大腸手術術前管理，蛋白漏出性胃腸炎

経腸栄養の利点

経腸栄養（Enteral Nutrition：EN）は経静脈栄養（Parenteral Nutrition：PN）に比して生理学的に経口摂取に近く，消化管ホルモン動態なども，より正常に維持することができる．また，合併症が少なく，より安全に管理することができる．近年，患者自身でチューブを挿入し，夜間だけの投与などをする在宅経腸栄養による社会復帰が可能になった．また長い期間，中心静脈栄養（Total Parenteral Nutrition：TPN）を用いると，小腸上皮粘膜の萎縮が生じて細菌のエンドトキシンが腸管粘膜を通過する現象（Bacterial Translocation）が起こる可能性が報告[2]されており，経腸栄養がこれを防止するとされている．

経腸栄養法の特徴

ENは，経鼻的に挿入したチューブや胃瘻・空腸瘻から栄養を注入する栄養法である．TPNの普及により，以前のような重要性を失ったかにみえたが，成分栄養剤（Elemental Diet：ED）や半消化態栄養剤の導入以後，ふたたびその有用性が強調されるようになってきた．また近年，外科的開腹を必要とせずに，内視鏡的に胃の内腔を確認しながら経皮的にチューブを挿入する経皮内視鏡的胃瘻造設術（PEG）が開発され，経口摂取不能の脳神経疾患患者などを中心に施行されるようになってきた．このように，栄養剤の開発とともに，チューブの材質や留置法にも改良が加えられ，現在ではPN（静脈栄養法）とともに非経口栄養の2本柱として広く利用されている．

経腸栄養剤の種類

原則的には，通常の食事では栄養摂取が十分ではないが腸管が機能しており，利用可能であれば経腸栄養を第一に考える．それ以外の場合は，PNを用い患者の消化吸収能の回復を待って，経腸栄養・経口栄養へと移行させていく．経腸栄養にはつぎの3種類あり，腸管の消化吸収能に応じて使い分ける．

①成分栄養
②半消化態栄養剤
③自然食品ミキサー食

経腸栄養法の適応と禁忌

一般に経腸栄養管理の適応となる病態は，経口摂取不能，あるいは困難で，かつ投与された栄養剤を消化，吸収することができる一定以上の長さの腸管がある場合である[3]．具体的には食道がん，胃がんなど上部消化管通過障害，大腸疾患の術前術後，炎症性腸疾患，縫合不全，消化管外瘻などが経腸栄養管理の主な適応である．これらはすべて静脈栄養法の適応と重複するが，基本的に腸管内投与が可能な例は第一選択として経腸栄養法とし，また，腸管を安静に保つことが好ましい，あるいは安静が必要な場合は静脈栄養法の適応と考えている．食思不振が長く続き，経口的に十分担取できない症例，合併療法施行例などはいずれの栄養法も適応があるが，可能な限り経腸栄養法を考慮すべきであろう．

経腸栄養剤投与スケジュール

経腸栄養法において，投与の開始時期，最高投

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表2　適切な投与エネルギー算出

Ⅰ．投与エネルギーの決め方（1日必要エネルギー量；kcal/日）
BEE×Activity Factor×Stress Factor
・Harris-Benedict の式：基礎エネルギー消費量（BEE；kcal/日）
男性：66.47＋13.75(W)＋5.0(H)－6.76(A)
女性：655.1＋9.56(W)＋1.85(H)－4.68(A)
W：体重（Kg）　H：身長（cm）　A：年齢
・Activity Factor
寝たきり　1.0　　歩行可　1..2
・Stress Factor
術後5日間
軽　度：1.2→胆嚢・総胆管切除，乳房切除
中等度：1.4→胃亜全摘，大腸切除
高　度：1.6→胃全摘，胆管切除
超高度：1.8→膵頭十二指腸切除，肝切除，食道切除
臓器障害→1.2＋1臓器につき0.2ずつup（4臓器以上は2.0）
熱　　傷→熱傷範囲10％ごとに0.2ずつup（Maxは2.0）
体　　温→1.0℃上昇→0.2ずつup
（37℃：1.2，38℃：1.4，39℃：1.6，40℃以上：1.8）

Ⅱ．たんぱく質必要量＝体重（kg）×Stress Factor

与に至る増量計画，投与速度などに関しては一定の方式はない．それぞれの患者の疾患や病態によって，経腸栄養投与スケジュールを計画すべきである．

原則として，低投与量から開始し，1週間以内に最高投与量にもっていく．

一般に肝・胆・膵疾患や大腸疾患の前後では，縫合不全のないことを確認したうえで経腸栄養を開始することが多いが，術後早期にまず，経管的に10％糖液を投与し発熱，腹部症状，あるいは下痢などの問題がなければ，成分栄養剤に移行し，その3－4日後には，病態に合わせた栄養剤に移行する．成分栄養剤は消化の必要がなく，ただちに吸収されることから，術後早期からの投与も可能である[4,5]．

一日投与量と投与回数

経腸栄養法には，間欠投与法と持続投与法がある．当然投与量が少ない場合は間欠投与が可能であるが，投与量が多くなると持続的に投与せざるをえなくなるため，投与初期段階では経腸栄養ポンプを用いた24時間持続投与法を選択し，時間当たりの投与量を少なくし，合併症を軽減することが推奨される[6]．この方法は常に血糖値が高く推移する弊害があるが，消化管耐性に有用で，とくに投与初期はこの方法が消化器症状の発生予防に一番よい．この際問題になるのは，調製した経腸栄養剤の腐敗である．栄養剤は調整，開封後6時間以上経過すると急速に細菌が増殖する．8時間以上経過したものは投与してはならない．したがって栄養剤をイルリガートルなどに移す場合には，6時間以内に投与が終了する量を入れ，開封した栄養剤の残量は破棄または冷所保存する[7]．

また，冷蔵庫から取り出した直後の冷えた栄養剤投与は下痢を招くことがあるが，しかし，投与直前に経腸栄養剤を温める行為により細菌が増殖するため加温の必要はなく，常温で十分である．

投与エネルギーは，Basal Energy Expenditure (BEE) に Activity Factor・Stress Factor を乗じた式を用いて各患者にエネルギー必要量を算出する（表2）．そしてBEEを基準として，身体計測値や栄養指標の推移，合併症などを考慮し投与エネルギー量を調節する．

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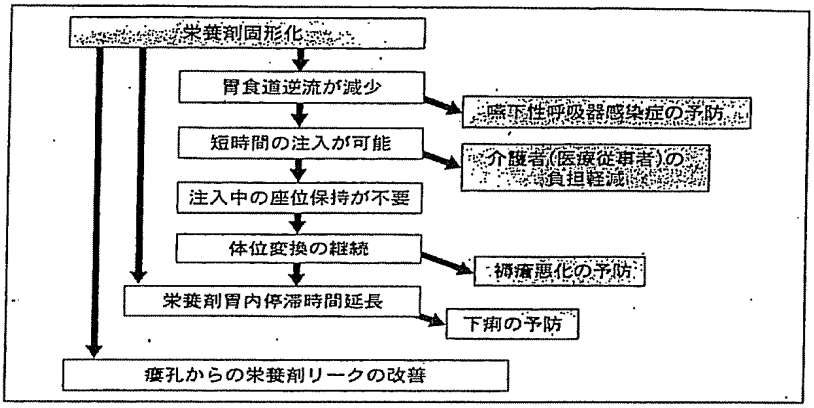

図2　経腸栄養剤固形化の効果
（盤江治郎：臨床栄養，104(6)：745，2002 より）

投与量と投与速度

筆者らの施設では，消化器の馴化をみて投与開始時で注入速度 40 m*l*/時間程度とし，200～400 kcal/日からスタートしている．その後，投与速度を徐々に増し，5～7日目には最高投与量の投与をめざし，速度を 100～120 m*l*/時間に到達させることを目標とする．空腸の対応できる生理的な浸透圧は，およそ 270～300 mOsm/*l* であるとされるが，経腸栄養剤の注入速度と注入量が過大であれば下痢の発生は避けられない．経腸栄養施行時に消化器症状をきたした場合には，注入速度を緩めてみることである[6]．

経腸栄養施行時においては，自然流動食，成分栄養剤，半消化態栄養剤のうちどれを用いても消化器系の副作用である悪心，嘔吐，腹部膨満，腹痛，下痢の発生頻度は変わらない．これら副作用発症の原因としては，浸透圧の異なる3種類の経腸栄養剤の投与によっても腹部症状が出現することから，経腸栄養剤の過剰な投与がもっとも関係すると考えられる．非手術例における自然流動食の短時間での大量投与や，手術後症例における成分栄養剤，あるいは半消化態栄養剤の過剰投与が消化吸収の限界を超えた結果として起こると考えられる．したがって，その対策としては止瀉剤などの投与よりも，まず栄養剤の注入速度でコントロールするのが最良の策であり，その後に薬物の投与を考慮すべきである．また，食物繊維を添加したり乳果オリゴ糖液を投与してみてもよい．しかし頻回の下痢が続く際には，一時，投与を中止して腸管の安静を保つ処置が必要となることもある．

経腸栄養剤固形化による GER 予防の効果

液体は固形物に比較して流動性が高く，噴門や幽門の通過が容易になるという問題点をもつ．栄養剤が噴門を容易に通過すれば胃食道逆流（Gastro Esophageal Reflux：以下 GER）となり，幽門の通過が多くなれば下痢の原因にもなりうる．また胃瘻症例においては，瘻孔からの栄養剤漏れである栄養剤リークの原因にもなる．経鼻胃管栄養で用いる栄養管は，PEG で用いる栄養管に比較して細径で長く，液体以外の注入は不可能である．しかし，PEG で用いる栄養管は経鼻胃管のものに比較して太径で短く，ゲル化した経腸栄養剤の注入が可能である．そこで盤江ら[8]は栄養剤をゲル化し“重力に抗してその形態が保たれる”硬さとしたものを“固形化経腸栄養剤”と定義し，液体経腸栄養剤より生理的で合併症の少ない方法とし

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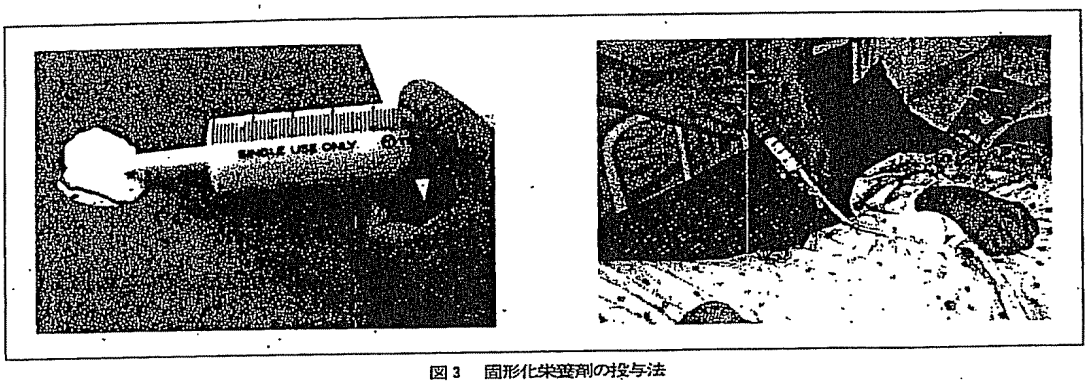

図3　固形化栄養剤の投与法

て報告を行っている．GERの予防としてはこれまでペクチンを用いて胃内で固形化する方法やポンプを使用して投与速度を遅延する方法が試みられてきた．この固形化経腸栄養剤を利用した経管栄養投与法は，PEGを利用して注入が可能な新しい経管栄養投与法の提案である（図2）．

1．固形化を行うため必要となる寒天の量[9]

固形化経腸栄養剤は栄養チューブを経由した注入を可能にするため，経口食品とは異なる量での調整が必要になる．蟹江[9]は経腸栄養剤を杏仁豆腐程度の硬さとするための寒天必要量として，希釈した栄養剤の総水分量200 mlに対して粉末寒天1 gを目安としている．しかし凝固の硬度は，栄養剤の成分や凝固する容器にも影響されるため，固形化栄養剤を実施する施設においては，実際に使用する栄養剤を使い，あらかじめ固形化調理を行って硬さの確認をする必要がある．

2．固形化経腸栄養剤の調理法[9]（図3）

固形化経腸栄養剤の調理は，寒天を溶解した溶液を経腸栄養剤と混合し，注入容器であるプラスチックシリンジに吸引した後に静置することで，短時間で簡便に行うことができる．経管栄養投与症例の多くは，経腸栄養剤の原液のみでの投与を行うと栄養過多になるため，一定量の水分で希釈して投与が行われることが多い．筆者らはこの希釈するための水分を，寒天溶液として調理を行っている．固形化栄養剤を行う症例での液体注入は，原則的に治療薬剤の溶解液分の水分量のみとしている．

3．固形化経腸栄養剤調理時の注意[9]

寒天を溶かした寒天溶液を調理する際の注意としては，粉末寒天をまず水に入れてなじませた後に加熱溶解することである．沸騰した熱湯に粉末寒天を入れると，寒天は“ダマ”になり溶解が困難になる．寒天は2分間の煮沸状態で十分な溶解が得られるため，煮沸時間についても注意が必要である．また寒天溶液と混合する経腸栄養剤は，あらかじめ人肌程度に加温しておく必要がある．栄養剤は冷たい状態で寒天溶液と混合すると，急速に冷却されることにより固形化が不均一になるため，注意を要する．

固形化については，有用性が期待され多くの施設で有益な結果をもたらしている．しかし，一部の施設では投与の際の看護師の拘束時間が問題となったり加熱によるビタミンの失活の是非[10,11]が問われ，今後も検討が必要だと思われる．

おわりに

いずれにせよPEGによる胃瘻造設に際しての栄養管理は造設前からはじまっており，造設後も患者の病態や病期，栄養状態を十分観察しNST

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(栄養サポートチーム)のようなチーム医療を通じて患者の栄養管理を行っていくことが重要である.

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TRANSLATION OF TREATISE NO.2

TITLE OF TREATISE: Monthly magazine "CLINICAL NUTRITION," Vol. 106, No. 3, written in Japanese, published March 2005

TITLE OF ARTICLE: "POST-PEG NUTRITION MANAGEMENT," pp.338-343 of this magazine

AUTHOR: Mr. Yasushi Miyazawa, a medical doctor

TRANSLATION OF RELEVANT EXCERPT:

GER PREVENTION EFFECTS DUE TO SEMI-SOLIDIFICATION OF ENTERAL NUTRITION PRODUCT

A liquid, which has higher fluidity than a solid, presents a problem that passing through the cardina and the pylorus becomes easier. Easier passing of a nutrition product through the cardina causes Gastro Esophageal Reflux (hereinafter, referred to as GER), and, if the nutrition product passes through the pylorus in an increased amount, also possibly causes diarrhea. In addition, in the case of gastric fistula, a nutrition leakage in which a nutrition product leaks through the stoma is also possibly caused. A feeding tube intended for use in nasogastric tube feeding, which is smaller in diameter and larger in length than a feeding tube intended for use in PEG, is incapable of the injection of a material other than a liquid. In contrast, a feeding tube intended for use in PEG, which is larger in diameter and smaller in length than that for use in nasogastric tube feeding, is capable of the injection of a gelled enteral nutrition. Then, Mr. Kanie, et al. define

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a "semi-solid enteral nutrition product" as a nutrition product which has been gelled so as to be so hard that "the nutrition product is self-sustaining against gravity," and they have reported such a nutrition product as a technique which is more physiological and less prone to cause complications than a liquid enteral nutrition product. Trials have been made for preventing GER, to solidify an enteral nutrition product within the stomach using pectin, and to decrease an administration rate using a pump. Transluminal nutrition feeding employing the semi-solid enteral nutrition product is a novel proposal of transluminal nutrition feeding allowing the injection of an enteral nutrition product in PEG (See Fig. 2).

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Practitioner's Docket No.: 889_001 *PATENT*

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of: Jiro Kanie

Serial No.:	10/826,165	Group Art Unit:	1618
Filed:	April 16, 2004	Examiner:	Young, Micah Paul
Conf. No.:	8549		

For: ENTERNAL NUTRITION PRODUCT AND METHOD FOR PREPARING THE SAME

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

CERTIFICATION OF EFS TRANSMISSION

I hereby certify that this paper is being transmitted via EFS to the Patent and Trademark Office on April 15, 2008.

Christina M. Bersani

DECLARATION UNDER 37 CFR §1.132

Sir:

I, Jiro Kanie, a citizen of Japan hereby declare and state:

1. I have a PhD. degree in medicine which was conferred upon me by Department of Geriatrics of Nagoya University Graduate School of Medicine, in 65 Tsurumai-cho, Showa-ku, 466-8550 Nagoya, Aichi, Japan, in 1998.

2. I have been running my own hospital since 2000, and I have had a total of 18 years of work and research experience in Geriatrics.

3. I am a member of :

- THE JAPAN GERIATRICS SOCIETY
- HOME HEALTH CARE, ENDOSCOPIC THERAPY AND QUALITY OF LIFE
- THE JAPANESE SOCIETY OF GASTROENTEROLOGY
- JAPAN GASTROENTEROLOGICAL ENDOSCOPY SOCIETY
- THE JAPANESE SOCIETY OF INTERNAL MEDICINE
- THE JAPAN MEDICAL ASSOCIATION

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4. I am the inventor of the above-identified patent application and I am familiar with the references applied in the Office Action mailed November 16, 2007.

5. The following is evidence of secondary considerations in support of patentability that the PTO must consider and which sufficiently to establishes the non-obviousness of the present invention.

(A) Corresponding Japanese Patent

Prior to the filing of the present U.S. patent application, I filed a corresponding Japanese patent application, which was allowed and issued as Japanese Patent No. 3516673. The JPO recognized the novelty and non-obviousness of the present invention.

(B) Existing Patent License

I have received offers to license my Japanese Patent from the Japanese pharmaceutical company "Otsuka Pharmaceutical Factory Inc. This company is one of the affiliates of Otsuka Pharmaceutical Co. Ltd. (see Appendix A attached hereto for more company information).

After successful negotiation, the Japanese Patent was licensed to Otsuka Pharmaceutical Factory, Inc. as a non-exclusive licensee, and the company received from the JPO, after request, a Patent Registration for the purpose of registering the grant of non-exclusive license. The original version of the Patent registration and an English translation thereof are attached hereto as Appendix B.

(C) Royalty Rate

The royalty rate on the sales applied to the licensee for the Japanese patent is 2%. This rate is about the average, and is expected to be larger compared to the cost of litigation, pre-license investigation by the licensees, etc. Therefore, the licensing considerations are persuasive in demonstrating that the licensee recognizes the novelty, non-obviousness and usefulness of the present invention, and also believes the Japanese patent is valid.

Indeed, the establishment of the licensing shows that the present invention has been recognized as being novel and commercially important in the related industry, and the validity of the Japanese patent is not easily challenged. The same holds true for the claimed invention in the present U.S. application, which is not obvious based on the prior art of record.

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(D) Ongoing Negotiation for additional Patent Licenses

Another Japanese company has made an offer for license of the above-stated Japanese patent. This company is "San-Ei Gen F.F.I., Inc." More information about this company is included in the attachment in Appendix C hereto.

That company has also shown a great interest with respect to its desire to practice the Japanese patent. We are presently in the course of negotiating a licensing agreement.

(E) Peer Recognition in the Related Field (publication of inventor's reports in U.S. medical treatises)

As indicated in the arguments which were presented to the U.S. PTO in the Amendment filed on August 29, 2005, the entire remarks of which are incorporated herein, I have co-authored several published reports on the claimed invention. Two of these reports were previously submitted to the U.S. PTO.

One of the two reports is titled "Prevention of Late Complications by Half-Solid Enternal Nutrients in Percutaneous Endiscopic Gastrostomy Tube Feeding," published on pp. 417-419 of the clinical section of Vol. 50, No. 6, 2004 of "Gerontology (International Journal of Experimental, Clinical and Behavioral Gerontology)," by Kerger Publishers. A copy of this article is attached as Appendix D hereto.

The other article is titled "Prevention of Gastro-Esophageal Reflux by an Application of Half-solid Nutrients in Patients with Perculaneous Endoscopic Gastronomy Feeding," published on pp. 466-467 of Vol. 52: Issue 3, March 2004 of "The Journal of the American Geriatrics Society," by Blackwell Publishing. A copy of this article is attached as Appendix E hereto.

(F) Long felt but unresolved need

As indicated in the specification of the present application, there has been a strong need to prevent dysphagic patients, especially elderly patients, from suffering from gastro-esophageal reflux when enternal nutrition products are administered to the patients via

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a tube. The need has been long felt, but has been heretofore unresolved. The present invention, however, solves this long felt need and has been academically praised and commercially recognized and implemented.

6. I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine and/or imprisonment under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing therefrom.

Date: April 15, 2004 Jiro Kanie

Jiro KANIE

Attachments: Appendices A-F

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Company Profile

I. Otsuka Pharmaceutical Factory, Inc.

a. Basic Information

Head Office :	115 Kuguhara, Tateiwa, Muya-cho, Naruto, Tokushima 772-8601, Japan
Phone :	+81-88-685-1151
Facsimile:	+81-88-685-7667
Established:	September 1, 1921
President:	Ichiro Ostuka
Capital:	80 million yen
Annual Sales:	95,510 million yen (as of September 30, 2005)
Number of Employee:	2,460 (as of September 30, 2005)
Business Description:	Manufacturing and sale of pharmaceutical and nutritional products

b. License Agreement

Licensed Patent	JP3516673 (which is substantially identical to the claimed invention in the present U.S. patent application)
Licensed Product	Enteral Nutrition Product
Target Customers for the Licensed Product	·patients with dysphagia ·elder people who have difficulty in swallowing
Royalty Rate	2% on the sales of the patented products
Term of This Agreement	from July 9, 2007 to July 9, 2010

Appendix A

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c. Patent Legacy Information

The Number of Patents (including Patent Applications)	1813 (from 1993 to 2008)
The Number of Patents (inluding Patent Applications) related to Enteral Nutrition Products	11 (from 1993 to 2008)

d. Additional Information

Parent Company:	Otsuka Pharmaceutical Co., Ltd.
Head Office :	2-9 Kanda-Tsukasamachi, Chiyoda-ku, Tokyo 101-8535, JAPAN
Phone :	+81-3-3292-0021
Established:	August 10, 1964
President:	Tatsuo Higuchi
Capital:	6.791 billion yen
Number of Employee:	5,225 (as of March 31, 2007)
Business Description:	Manufacturing, distributing, exporting, and importing of pharmaceuticals, clinical testing equipment, medical equipment, food products, cosmetics, and other related products
Business Premises	17 branch offices, 51 district offices (in Japan)
Reserch Facilities	18 divisions in 5 locations
Clinical Research	2 divisions
Factories	6 locations

Appendix A

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(translation)

Notice of Patent Registration

(seal)
Japan Patent Office

Date of Acceptance: November 2, 2007
Acceptance No.: 009867
Person Entitled to the Registration: Otsuka Pharmaceutical Factory, Inc.
Registered on: November 15, 2007

Note

Item Number	Patent Number	Supplementary Note	Purpose
1	JP3516673	001	【Grant of Non-Exclusive License】

ADDRESS MARUNOUCHI ESTATE BLDG., SUITE 403
2-17-12 MARUNOUCHI, NAKA-KU,
NAGOYA-SHI, JAPAN 460-0002

NAME KAZUNORI KURUSU

Made on: November 15, 2007

00037

Appendix B

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特許登録済通知書

特許庁

受付年月日　平成１９年１１月　２日　　受付番号　００９８６７

登録権利者　株式会社大塚製薬工場

平成１９年１１月１５日　登録

記

項番	特許番号	順位付記	目的
1	３５１６６７３	001	【通常実施権の設定】

〒４６０－０００２

住所　愛知県名古屋市中区丸の内２－１７－１２　丸の内エステートビル４０３号

氏名　来栖和則　　様

平成１９年１１月１５日　作成　　00037

Appendix B

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Company Profile

Ⅱ. San-Ei Gen F.F.I., Inc.

a. Basic Information

Head Office :	1-4-9, Hirano-machi, Chuo-ku, Osaka 540-8688 JAPAN
Phone :	+81-6-6202-3751
Facsimile:	+81-6-6202-3770
Established:	September, 1938
President:	Takashige Shimizu
Capital:	1,800 million yen
Annual Sales:	64,800 million yen (April 2005 - March 2006))
Products & Servuces:	Food ingredients, Foods, Food materials, Quasi-drugs, Industrial chemicals

b. Patent Legacy Information

The Number of Patents (including Patent Applications)	1,054 (from 1993 to 2008)
The Number of Patent (including Patent Applications) related to a semi-solidifying agent	119 (from 1993 to 2008)

Appendix C

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Gerontology

Clinical Section

Gerontology 2004;50:417–419
DOI: 10.1159/000080181

Received: August 12, 2003
Accepted: February 15, 2004

Prevention of Late Complications by Half-Solid Enteral Nutrients in Percutaneous Endoscopic Gastrostomy Tube Feeding

Jiro Kanie[a] Yusuke Suzuki[a] Hiroyasu Akatsu[b] Masafumi Kuzuya[a] Akihisa Iguchi[a]

[a]Department of Geriatrics, Medicine in Growth and Aging, Program in Health and Community Medicine, Nagoya University Graduate School of Medicine, Nagoya, and [b]Department of Internal Medicine, Fukushimura Hospital, Toyohashi, Japan

Key Words
Percutaneous endoscopic gastrostomy · Enteral nutrients, half-solid · Gastroesophageal reflux

Abstract
Background: Percutaneous endoscopic gastrostomy feeding is accompanied by unique complications, which are not easily controlled. ***Objective:*** In an attempt to decrease complications, we used half-solid nutrients for percutaneous endoscopic gastrostomy feeding in an 85-year-old woman. The patient had been receiving enteral nutrients via percutaneous endoscopic gastrostomy, and we examined whether this approach can reduce complications. She presented with regurgitation of enteral nutrients and recurrent respiratory infections. ***Methods:*** Half-solid enteral nutrients, prepared by mixing liquid enteral nutrients with agar powder, were administered via percutaneous endoscopic gastrostomy. ***Results:*** Symptoms of gastroesophageal reflux disappeared immediately after the start of half-solid enteral nutrient feeding. ***Conclusion:*** Gastroesophageal reflux and leakage, two intractable late complications of percutaneous endoscopic gastrostomy tube feeding, can be alleviated by the solidification of enteral nutrients. Since this method allows quick administration of nutrients, it is also expected to help prevent the occurrence of decubitus ulcers and reduce the burden to the caregiver.

Introduction

Feeding via a percutaneous endoscopic gastrostomy (PEG) tube is a safe and efficient method for patients who cannot maintain adequate oral intake. PEG feeding is accompanied, however, by unique complications which are not easily controlled. The administration of liquid nutrients is often accompanied by complications such as vomiting and diarrhea, although these complications may be minimized if the patient is sitting up during the administration or if the nutrients are administered at a slower rate. Nevertheless, these methods do not completely succeed in eliminating these common complications, and may require the patients and their caregivers to have great patience. In addition, maintaining the same position for many hours may worsen the conditions of patients who have pressure ulcers. Here we report a case in which, by

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Appendix D

APPENDIX B2

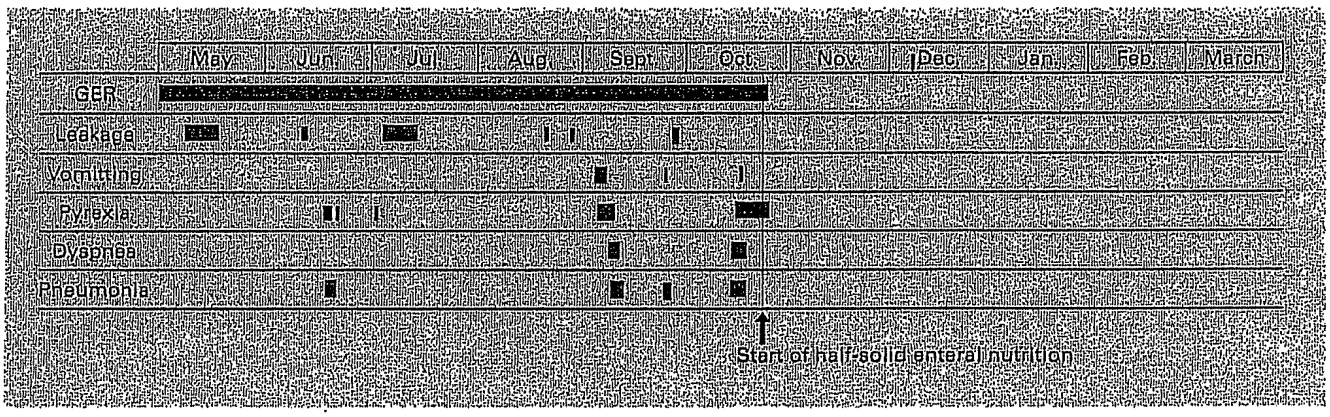

Fig. 1. Reduction of symptoms after half-solid enteral nutrition via PEG.

simply solidifying nutrients, the symptoms due to gastroesophageal reflux (GER) after PEG tube placement were relieved, and the leakage of nutrients from the PEG tube insertion site was alleviated.

Methods

An 85-year-old woman presented with regurgitation of enteral nutrients and recurrent respiratory infections after PEG placement. The patient suffered a cerebral infarction, and underwent PEG insertion on May 4, 2001, at a local hospital. After commencing PEG tube feeding, the following symptoms repeatedly occurred: regurgitation of the enteral feed; leakage of nutrients from the PEG tube insertion site; vomiting followed by pyrexia; dyspnea during the administration of nutrients, and pneumonia confirmed by chest X-ray. The patient often showed facial signs of discomfort during the feed administration. Liquid enteral nutrients were given in a sitting position at all times.

As the complications gradually became more frequent in occurrence, on October 21, 2001, we commenced giving her half-solid enteral nutrients which were prepared by mixing market-available enteral nutrients and agar powder. Half-solid nutrients were prepared by mixing 5 g agar powder with 500 ml liquid nutrients diluted with the same volume of water (1,000 ml total volume). The mixture was distributed into 50-ml syringes and kept in a refrigerator until it was administered via the PEG tubing. The mixture was not liquefied in the stomach due to body temperature. The administration of half-solid nutrients was made by injecting them into the stomach en bloc (injection time <5 min). The patient was not forced to remain in a sitting position during and after the administration.

Results

The symptoms, other than pyrexia, disappeared immediately after the administration of half-solid nutrients, and pyrexia vanished 2 weeks later. Also, the signs of discomfort during the feed administration were no longer noted. We followed the patient for up to 6 months after the start of the half-solid enteral nutrients, and observed no recurrence of the symptoms (fig. 1). At present (February 2004), the patient still remains in a stable condition and no longer suffers from the complications observed before the commencement of half-solid nutrients.

Discussion

PEG feeding is accompanied by unique complications, which occur over a long-term clinical course [1–3]. An increase in vomiting is one of the most common complications [4]. GER is clinically manifested by recurrent vomiting or aspiration. The mechanism by which GER increases in frequency has not yet been clarified.

Ogawa et al. [5, 6] suggested that since the stomach cannot move independent of the abdominal wall after the formation of a gastric fistula, enteral nutrients remain in the stomach longer, thereby increasing the chance of GER. Gastrin, a potent facilitator of peristaltic movement, may not be sufficiently induced by the distension of the stomach seen with slow infusion rates of liquid nutrients. Thus enhanced GER may eventually result. Since the nutrients can be administered in a short time by

Appendix D

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our method (<5 min), the stomach wall is expected to be distended to a greater degree and thus stimulate peristaltic movement.

Another disadvantage of slow feed infusion is that patients are forced to remain in a sitting position for long periods while the nutrients are administered, which is unfavorable in terms of the prevention of decubitus ulcers, which are commonly found in patients with PEG feeding.

One of the late complications after PEG tube placement is leakage from the PEG tube insertion site. This is a difficult problem to cope with. There are two causes of leakage: inappropriate fixation of the bumper (including the so-called buried bumper syndrome [7]), and a decrease in the elasticity of the fistular opening, which develops over a long period after PEG placement [8]. The leakage resulting from a decrease in elasticity is intractable. Simply increasing the tube diameter cannot solve this problem [7, 9]. We found, however, that solidification of the enteral nutrients alleviated the leakage in the present case. This may simply be explained by the fact that the solidified nutrients could not be leaked out by the intragastric pressure through the narrow gap between the fistular pore and the tube.

So far, we have administered half-solid nutrients to 17 patients with PEG feeding and followed up the patients for 6 months. During the observation period, we confirmed significant reductions in the complications observed before the commencement of the half-solid nutrients (data not shown).

In conclusion, our experience indicates that the use of half-solid nutrients in PEG feeding and their rapid administration can substantially reduce the risk of GER and may eventually contribute to a reduction in complications as well as an improvement in the quality of life of the patients and their caregivers.

References

1 Dwolatzky T, Berezovski S, Friedmann R, et al: A prospective comparison of the use of nasogastric and percutaneous endoscopic gastrostomy tubes for long-term enteral feeding in older people. Clin Nutr 2001;20:535–540.

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Appendix D

APPENDIX B2

Prevention of gastro-esophageal reflux by an application of half-solid nutrients in patients with percutaneous endoscopic gastrostomy feeding

Jiro Kanie, MD, PhD*, Yusuke Suzuki*, MD, PhD, Hiroyasu Akatsu, MD, PhD, Hiroshi Shimokata***, MD, PhD, Takayuki Yamamoto**, MD, PhD, Akihisa Iguchi* MD, PhD**

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** Department of Internal Medicine Fukushimura Hospital, 19-14, Yamanaka, Noyori-cho, Toyohashi, Aichi, 441-8124, Aichi, Japan (Hiroyasu Akatsu, M.D., Takayuki Yamamoto, M.D.)

*** Department of Epidemiology National Institute for Longevity Sciences, Morioka-cho Gengo 36-3, Obu-shi, 474-8522, Aichi, Japan (Hiroshi Shimokata, M.D.)

To the Editor: Although percutaneous endoscopic gastrostomy (PEG) feeding is widely used as a convenient method for long-term nutritional support[1], administration of liquid nutrients is often accompanied by complications such as vomiting or diarrhea. Vomiting, which may result in critical condition by aspiration, is presumably caused by gastro-esophageal reflux (GER). Therefore, we used half-solid nutrients for PEG feeding and examined whether this approach can reduce GER.

Seventeen patients (mean age $\pm$ SD; 79.9 $\pm$ 10.5), who were on PEG feeding participated in this study. Written informed consent was obtained from all patients. Either liquid or half-solid nutrients were administered via PEG tubing in a randomized order. Half-solid nutrients were prepared by mixing 5g of agarose with 500ml of liquid nutrients diluted with the same volume of water. Incidence of GER was assessed by computed tomography scan (CT) of the esophagus. Liquid nutrients were administered over 15 minutes in portions of 400ml containing 20ml of the water-soluble contrast material, Gastrografin (methylglucamine diatrizonate). The half-solid nutrients were administered by bolus injections of the same volume of nutrients, which were contained separately in 50ml syringes. Thirty minutes after the administration, CT scan was performed in 1cm thick slices of the esophageal portion. GER was confirmed if the Hounsfield number exceeded 100 in each slice examined. A Hounsfield number of 100 was employed because it can unequivocally distinguish the mixture of the nutrients containing contrast material from the esophageal and other surrounding tissues. The CT images were assessed by a radiologist, who was not informed of the type of nutrients used. Statistical comparison of the incidence of GER between the two types of nutrients was made using Mc Nemar's test.

GER was confirmed in 10 out of the 17 subjects (58.8%) when they received liquid nutrients. By contrast, when they received half-solid nutrients, only 4 of 17 subjects (23.5%) showed the evidence of GER from their CT findings. ($\chi^2 = 6.0$, df = 1, p = 0.014, by Mc Nemar's test) (Table 1).

The advantages of PEG feeding over nasogastric feeding has been discussed elsewhere albeit there have been some complications reported.[2] Among the complications, vomiting can be a cause of fatal aspiration due to a reflux of the administered nutrients.[3] The tubing used for PEG feeding has made it possible to apply half-solidified nutrients, which we hypothesized would cause less reflux from the stomach.[4] As expected, we observed less evidence of GER when using half-solid nutrients than when using liquid nutrients. We also confirmed that solidifying nutrients using agarose did not clog the tube as compared to liquid nutrients. Continuous infusion and careful observation of the patient's symptoms are considered necessary to reduce the risk of GER in PEG feeding. Also the patients are advised to remain in a sitting position during administration, which

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may increase the risk of developing or exacerbating decubitus ulcers. Thus, this pilot study suggests that the use of rapid administration of half-solid nutrients in PEG feeding can reduce the risk of GER substantially, and may eventually contribute to a reduction of complications as well as to the improvement in the quality of life for patients and their cargivers.

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Table 1. Occurrence of gastro-esophageal reflux by liquid and half-solid nutrients

Age	Sex	Clinical profile	gastro-esophageal reflux		Range of reflux		Distance from the EC junction	
			Liquid	Half-solid	Liquid	Half-solid	Liquid	Half-solid
82	F	Dementia	(-)	(-)				
81	F	Dementia	(-)	(-)				
90	F	Dementia	(+)	(+)	7	6	13	13
53	F	Cerebral infarction	(-)	(-)				
87	F	Dementia	(+)	(-)	4		13	
80	F	Dementia	(+)	(+)	9	4	9	10
82	M	Dementia	(+)	(+)	4	4	13	13
87	F	Cerebral infarction	(+)	(-)	1		4	
84	M	Cerebral infarction	(+)	(-)	12		15	
68	F	Cerebral infarction	(+)	(-)	13		13	
82	F	Dementia	(-)	(-)				
89	F	Cerebral infarction	(-)	(-)				
91	F	Cerebral infarction	(+)	(-)	1		2	
84	F	Cerebral infarction	(+)	(+)	15	10	15	10
87	F	Dementia	(-)	(-)				
68	M	Cerebral infarction	(-)	(-)				
64	M	Cerebral hemorrhage	(+)	(-)	5		8	
			10 (58.8%)	4 (23.5%)*				

Range of reflux: Number of slices where contrast materials were confirmed in the esophagus
Distance from the EC junction:
Distance from the esophageal-cardiac junction to the upper limit of the slices where contrast materials were confirmed (cm)
* Statistical significance by Mc Nemar's test ($\chi^2 = 6.0$; df = 1, p = 0.014)

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APPENDIX B3

may increase the risk of developing or exacerbating decubitus ulcers. Thus, this pilot study suggests that the use of rapid administration of half-solid nutrients in PEG feeding can reduce the risk of GER substantially, and may eventually contribute to a reduction of complications as well as to the improvement in the quality of life for patients and their cargivers.

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APPENDIX B3

Clinical Section

Gerontology

Gerontology 2004;50:417–419
DOI: 10.1159/000080181

Received: August 12, 2003
Accepted: February 16, 2004

Prevention of Late Complications by Half-Solid Enteral Nutrients in Percutaneous Endoscopic Gastrostomy Tube Feeding

Jiro Kanie[a] Yusuke Suzuki[a] Hiroyasu Akatsu[b] Masafumi Kuzuya[a] Akihisa Iguchi[a]

[a]Department of Geriatrics, Medicine in Growth and Aging, Program in Health and Community Medicine, Nagoya University Graduate School of Medicine, Nagoya, and [b]Department of Internal Medicine, Fukushimura Hospital, Toyohashi, Japan

Key Words
Percutaneous endoscopic gastrostomy · Enteral nutrients, half-solid · Gastroesophageal reflux

Abstract
Background: Percutaneous endoscopic gastrostomy feeding is accompanied by unique complications, which are not easily controlled. ***Objective:*** In an attempt to decrease complications, we used half-solid nutrients for percutaneous endoscopic gastrostomy feeding in an 85-year-old woman. The patient had been receiving enteral nutrients via percutaneous endoscopic gastrostomy, and we examined whether this approach can reduce complications. She presented with regurgitation of enteral nutrients and recurrent respiratory infections. ***Methods:*** Half-solid enteral nutrients, prepared by mixing liquid enteral nutrients with agar powder, were administered via percutaneous endoscopic gastrostomy. ***Results:*** Symptoms of gastroesophageal reflux disappeared immediately after the start of half-solid enteral nutrient feeding. ***Conclusion:*** Gastroesophageal reflux and leakage, two intractable late complications of percutaneous endoscopic gastrostomy tube feeding, can be alleviated by the solidification of enteral nutrients. Since this method allows quick administration of nutrients, it is also expected to help prevent the occurrence of decubitus ulcers and reduce the burden to the caregiver.

Introduction

Feeding via a percutaneous endoscopic gastrostomy (PEG) tube is a safe and efficient method for patients who cannot maintain adequate oral intake. PEG feeding is accompanied, however, by unique complications which are not easily controlled. The administration of liquid nutrients is often accompanied by complications such as vomiting and diarrhea, although these complications may be minimized if the patient is sitting up during the administration or if the nutrients are administered at a slower rate. Nevertheless, these methods do not completely succeed in eliminating these common complications, and may require the patients and their caregivers to have great patience. In addition, maintaining the same position for many hours may worsen the conditions of patients who have pressure ulcers. Here we report a case in which, by

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APPENDIX B4

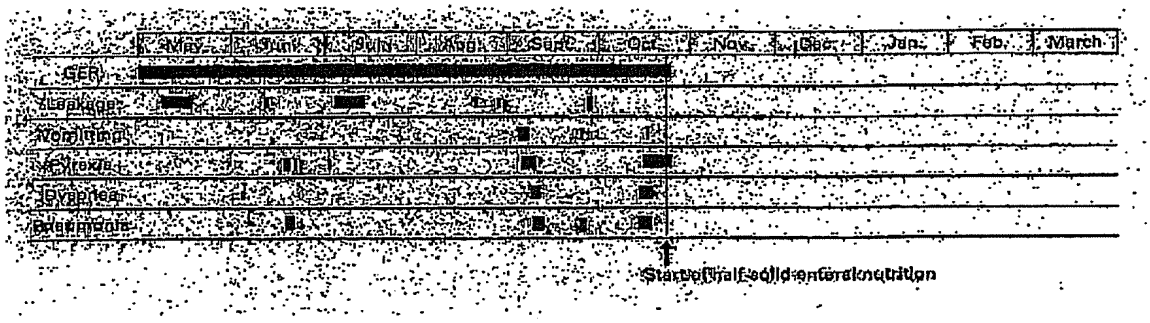

Fig. 1. Reduction of symptoms after half-solid enteral nutrition via PEG.

simply solidifying nutrients, the symptoms due to gastroesophageal reflux (GER) after PEG tube placement were relieved, and the leakage of nutrients from the PEG tube insertion site was alleviated.

Methods

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As the complications gradually became more frequent in occurrence, on October 21, 2001, we commenced giving her half-solid enteral nutrients which were prepared by mixing market-available enteral nutrients and agar powder. Half-solid nutrients were prepared by mixing 5 g agar powder with 500 ml liquid nutrients diluted with the same volume of water (1,000 ml total volume). The mixture was distributed into 50-ml syringes and kept in a refrigerator until it was administered via the PEG tubing. The mixture was not liquefied in the stomach due to body temperature. The administration of half-solid nutrients was made by injecting them into the stomach en bloc (injection time <5 min). The patient was not forced to remain in a sitting position during and after the administration.

Results

The symptoms, other than pyrexia, disappeared immediately after the administration of half-solid nutrients, and pyrexia vanished 2 weeks later. Also, the signs of discomfort during the feed administration were no longer noted. We followed the patient for up to 6 months after the start of the half-solid enteral nutrients, and observed no recurrence of the symptoms (fig. 1). At present (February 2004), the patient still remains in a stable condition and no longer suffers from the complications observed before the commencement of half-solid nutrients.

Discussion

PEG feeding is accompanied by unique complications, which occur over a long-term clinical course [1–3]. An increase in vomiting is one of the most common complications [4]. GER is clinically manifested by recurrent vomiting or aspiration. The mechanism by which GER increases in frequency has not yet been clarified.

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APPENDIX B4

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APPENDIX B4

01-25-05

IFW

OIPE JAN 24 2005 USPTO PATENT & TRADEMARK OFFICE

PATENT AMENDMENT TRANSMITTAL

(Provisions of 37 CFR 1.136 Apply)

Application Number	10/826,165	Filing Date	April 16, 2004
Group Art Unit	1615	Examiner Name	Young, Micah Paul
Confirmation No.	8549	Attorney Docket No.	889_001
Inventor(s)	Jiro KANIE		
Invention:	ENTERAL NUTRITION PRODUCT AND METHOD FOR PREPARING THE SAME		

Transmitted herewith is an Amendment in the above-identified application. The fee has been calculated as follows:

CLAIMS AS AMENDED

(1)	(2) Claims Remaining After Amendment	(3)	(4) Highest Number Previously Paid	(5) No. of Extra Claims Present	(6) Rate (Large Entity)	(7) Additional Fee
TOTAL CLAIMS	6	MINUS	20		$ 50.00	$00.00
INDEPENDENT CLAIMS	1	MINUS	3		$ 200.00	$00.00
TOTAL ADDITIONAL FEE FOR THIS AMENDMENT						$00.00

EXTENSION OF TERM

☐ Applicant believes that no extension of term is required. However, this conditional petition is being made to provide for the possibility that applicant has inadvertently overlooked the need for a petition for extension of time.

☒ This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above-identified application. The requested extension and appropriate non-small entity fee are as follows:

☒ One Month (37 CFR 1.17(a)(1) $120.00	120.00
☐ Two Month (37 CFR 1.17(a)(2) $450.00	
☐ Three Month (37 CFR 1.17(a)(3) $1,020.00	
TOTAL FEES DUE	$120.00
☒ Applicant claims small entity status. See 37 CFR 1.27. Therefore, the fee amount is reduced by one-half, and the resulting fee is:	$60.00

FEE PAYMENT

☐ No additional fee is required. ☒ A check in the amount of $60.00 is enclosed.

☐ Charge Deposit Account 50-1446 in the amount of $_____. Enclosed is a duplicate copy of this sheet.

☒ Please charge any fees which may be required, or credit any overpayment, to Deposit Account 50-1446.

Submitted By:

Name *(Print Type)*	Nicole J. Buckner	Reg. No.	51,508	Customer No.	025191
		Telephone	(315) 233-8300	Facsimile	(315) 233-8320
Signature	/NJBuckner/			Date	January 24, 2005

EXPRESS MAIL CERTIFICATE

"Express Mail" label number EV 373084631 US

Date of Deposit: January 24, 2005

I hereby certify that this correspondence is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR § 1.10, on the date indicated above and is addressed to the **M.S. Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

/GMHusak/

Gina M. Husak

APPENDIX B4

Related Proceeding Appendix
(37 CFR § 41.37 (c)(1)(x))

None